

CLAIMS

1. Pharmaceutical compositions comprising one or several agents as compound I
which modulate the biological function of one or several of the VEGF/VEGF

5 receptor systems, and comprising one or several agents as compound II which
modulate the biological function of one or several of the Angiopoietin/Tie
receptor systems.

10 2. Pharmaceutical compositions comprising one or several agents as compound I
which are targeted to the endothelium via of one or several of the VEGF/VEGF
receptor systems, and comprising one or several agents as compound II which
modulate the biological function of one or several of the Angiopoietin/Tie
receptor systems.

15 3. Pharmaceutical compositions comprising one or several agents as compound I
which modulates the biological function of one or several of the VEGF/VEGF
receptor systems or of one or several of the Angiopoietin/ Tie receptor systems
and comprising one or several agents as compound II which are targeted to
the endothelium.

20 4. Pharmaceutical compositions comprising one or several agents as compound I
which modulate the biological function of one or several of the VEGF/VEGF
receptor systems, and comprising one or several agents as compound II which
are targeted to the endothelium via one or several of the Angiopoietin/Tie
receptor systems.

25 5. Pharmaceutical compositions comprising one or several agents as compound I
which are targeted to the endothelium via one or several of the VEGF/VEGF
receptor systems, and comprising one or several agents as compound II which
are targeted to the endothelium via one or several of the Angiopoietin/Tie
receptor systems.

30 6. Pharmaceutical compositions comprising one or several agents as compound
I which modulate the biological function of one or several of the VEGF/VEGF

receptor systems, and comprising one or several agents as compound II which are targeted to the endothelium via one or several of the VEGF/VEGF receptor systems.

- 5 7. Pharmaceutical compositions comprising one or several agents as compound I which modulate the biological function of one or several of the Angiopoietin/Tie receptor systems, and comprising one or several agents as compound II which are targeted to the endothelium via one or several of the Angiopoietin/Tie receptor systems.
- 10 8. Pharmaceutical compositions comprising one or several agents which interfere with both the function of one or several of the VEGF/VEGF receptor systems and the function of one or several of the Angiopoietin/Tie receptor systems.
- 15 9. Pharmaceutical compositions according to claims 1-8 which are intended for simultaneous or separate sequential therapeutical application.
10. Pharmaceutical compositions according to claims 1-8 which comprise as compound I at least one of
- 20 a) compounds which inhibit receptor tyrosine kinase activity,
b) compounds which inhibit ligand binding to receptors,
c) compounds which inhibit activation of intracellular signal pathways of the receptors,
d) compounds which inhibit or activate expression of a ligand or of a
25 receptor of the VEGF or Tie receptor system,
e) delivery systems, such as antibodies, ligands, high-affinity binding oligonucleotides or oligopeptides, or liposomes, which target cytotoxic agents or coagulation-inducing agents to the endothelium via recognition of VEGF/VEGF receptor or Angiopoietin/Tie receptor systems,
- 30 f) delivery systems, such as antibodies, ligands, high-affinity binding oligonucleotides or oligopeptides, or liposomes, which are targeted to the endothelium and induce necrosis or apoptosis.

11. Pharmaceutical compositions according to claims 1-8 which comprise as compound II at least one of

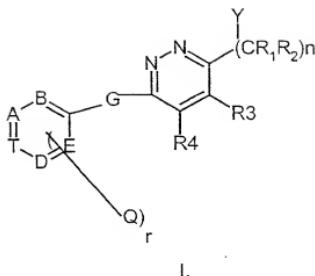
- g) compounds which inhibit receptor tyrosine kinase activity,
- h) compounds which inhibit ligand binding to receptors,
- 5 i) compounds which inhibit activation of intracellular signal pathways of the receptors,
- j) compounds which inhibit or activate expression of a ligand or of a receptor of the VEGF or Tie receptor system,
- k) delivery systems, such as antibodies, ligands, high-affinity binding oligonucleotides or oligopeptides, or liposomes, which target cytotoxic agents or coagulation-inducing agents to the endothelium via recognition of VEGF/VEGF receptor or Angiopoietin/Tie receptor systems,
- 10 l) delivery systems, such as antibodies, ligands, high-affinity binding oligonucleotides or oligopeptides, or liposomes, which are targeted to the endothelium and induce necrosis or apoptosis.

12. Pharmaceutical compositions according to claims 1-11 which comprise as compound I and/ or II at least one of Seq. ID Nos. 1-59.

20 13. Pharmaceutical compositions according to claims 1-11 which comprise as compound I and/ or II Seq. ID Nos. 34a

14. Pharmaceutical compositions according to claims 1-11 which comprise as compound I and/ or II at least one of sTie2, mAB 4301-42-35, scFv-tTF and/ or L19 scFv-tTFconjugate.

30 15. Pharmaceutical compositions according to claims 1-11 which comprise as compound I and/ or II at least one small molecule of genaral formula I



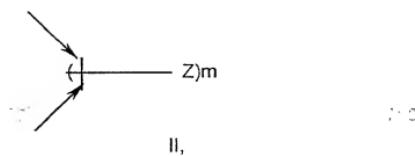
in which

r has the meaning of 0 to 2,

n has the meaning of 0 to 2;

R₃ und R₄

- a) each independently from each other have the meaning of lower alkyl,
- b) together form a bridge of general partial formula II,



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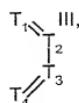
wherein the binding is via the two terminal C- atoms,
and

m

has the meaning of 0 to 4; or

c) together form a bridge of partial formula III

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has

wherein one or two of the ring members T₁, T₂, T₃, T₄ has the meaning of nitrogen, and each others have the meaning of CH, and the bining is via the atoms T₁ and T₄;

G

has the meaning of C₁ -C₆ - alkyl, C₂ - C₆ – alkylene or C₂ - C₆ – alkenylene; or C₂ - C₆ - alkylene or C₃ -C₆- alkenylene, which are substituted with acyloxy or hydroxy; -CH₂-O-, -CH₂-S-, -CH₂-NH-, -CH₂-O-CH₂-, -CH₂-S-CH₂-, -CH₂-NH-CH₂, oxa (-O-), thia (-S-) or imino (-NH-),

A, B, D, E and T

independently from each other have the meaning of N or CH , with the provisio that not more than three of these Substituents have the meaning of N,

Q

has the meaning of lower alkyl, lower alkyloxy or halogene,

R₁ and R₂

independently from each other have the meaning of H or lower alkyl,

X

has the meaning of imino, oxa or thia;

Y

has the meaning of hydrogen, unsubstituted or substituted aryl, heteroaryl, or unsubstituted or substituted cycloalkyl; and

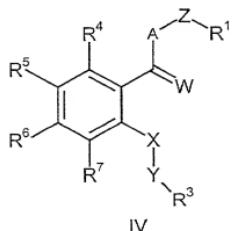
Z

has the meaning of amino, mono- or disubstituted amino, halogen, alkyl, substituted alkyl, hydroxy, etherificated or esterificated hydroxy, nitro, cyano, carboxy, esterificated carboxy, alkanoyl, carbamoyl, N-mono- or N, N- disubstituted carbamoyl, amidino, guanidino, mercapto, sulfo, phenylthio, phenyl-lower-alkyl-thio, alkyl-phenyl-thio, phenylsulfinyl, phenyl-lower-alkyl-sulfinyl, alkylphenylsulfinyl, phenylsulfonyl, phenyl-lower-alkan-sulfonyl, or alkylphenylsulfonyl, whereas, if more than one rest Z is present ($m \geq 2$), the substituents Z are equal or different from each other, and wherein the bonds marked with an arrow are single

or double bonds; or an N-oxide of said compound,
wherein one or more N-atoms carry an oxygen atom,
or a salt thereof,

and/or a compound of general formula IV

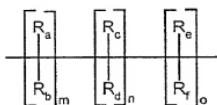
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in which

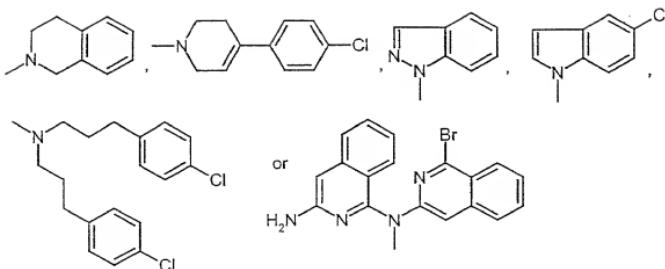
- A has the meaning of group $=NR^2$,
- W has the meaning of oxygen, sulfur, two hydrogen atoms or the group $=NR^8$,
- Z has the meaning of the group $=NR^{10}$ or $=N-, -N(R^{10})-(CH_2)_q-$, branched or unbranched C₁₋₆-Alkyl or is the group

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or A, Z and R¹ together form the group

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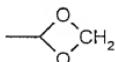
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m, n and o	has the meaning of 0 – 3,
q	has the meaning of 1 – 6,
R _a , R _b , R _c , R _d , R _e , R _f	independently from each other have the meaning of hydrogen, C ₁₋₄ alkyl or the group =NR ¹⁰ , and/or R _a and/or R _b together with R _c and/or R _d or R _e together with R _e and/or R _f form a bound, or up to two of the groups R _a -R _f form a bridge with each up to 3 C-atoms with R ¹ or R ² ,
X	has the meaning of group =NR ⁹ or =N-,
Y	has the meaning of group -(CH ₂) _p ,
p	has the meaning of integer 1-4,
R ¹	has the meaning of unsubstituted or optionally substituted with one or more of halogene, C ₁₋₆ -alkyl, or C ₁₋₆ -alkyl or C ₁₋₆ -alkoxy, which is optionally substituted by one or more of halogen, or is unsubstituted or substituted aryl or heteroaryl,
R ²	has the meaning of hydrogen or C ₁₋₆ -alkyl, or form a bridge with up to 3 ring atoms with R _a -R _f together with Z or R ₁ ,
R ³	has the meaning of monocyclic or bicyclic aryl or heteroaryl which is unsubstituted or optionally

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 R^4, R^5, R^6 and R^7

substituted with one or more of für halogen, C₁₋₆-alkyl, C₁₋₆-alkoxy or hydroxy, independently from each other have the meaning of hydrogen, halogene or C₁₋₆-alkoxy, C₁₋₆-alkyl or C₁₋₆-carboxyalkyl, which are unsubstituted or optionally substituted with one or more of halogene, or R^5 and R^6 together form the group



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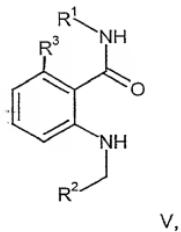
 R^8, R^9 and R^{10}

independently from each other have the meaning of hydrogen or C₁₋₆-alkyl, as well as their isomers and salts,

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and/ or a compound of general formula V

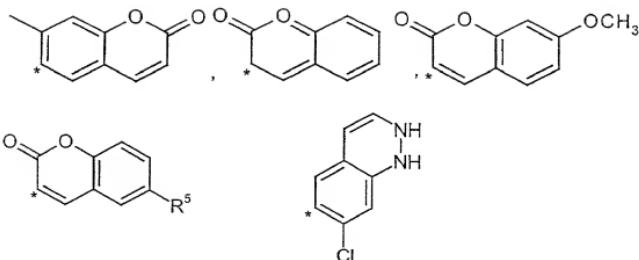
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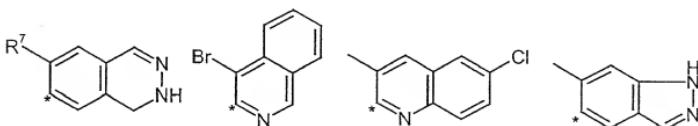
V,

in which

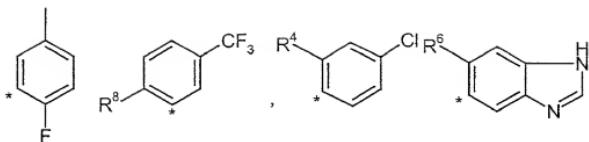
 R^1 has the meaning of group



in which R⁵ is chloro, bromo or the group -OCH₃,



in which R⁷ is -CH₃ or chloro.



in which R⁸ is -CH₃, fluoro, chloro or -CF₃

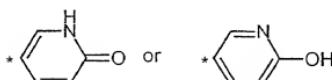
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in which R⁴ is fluoro, chloro, bromo, -CF₃, -N=C, -CH₃, -OCF₃ or -CH₂OH

in which R⁶ is -CH₃ or chloro

R²

has the meaning of pyridyl or the group



and

R³

has the meaning of hydrogen or fluoro, as well as their isomers and salts.

16. Pharmaceutical compositions according to claim 15 which comprise as

15 compound I and/ or II (4-Chlorophenyl)[4-(4-pyridylmethyl)-phthalazin-1-yl]ammonium hydrogen succinate

17. Pharmaceutical compositions according to claims 1-16 which comprise as

compound I (4-Chlorophenyl)[4-(4-pyridylmethyl)-phthalazin-1-yl]ammonium hydrogen succinate, sTie2, mAB 4301-42-35, scFv-tTF and/ or L19 scFv-tTF conjugate, and as compound II (4-Chlorophenyl)[4-(4-pyridylmethyl)-phthalazin-1-yl]ammonium hydrogen succinate Tie2, mAB 4301-42-35, scFv-tTF and/ or L19 scFv-tTF conjugate, with the provisio that compound I is not identically to compound II.

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18. Pharmaceutical compositions according to claims 1-17 which comprise as compound I (4-Chlorophenyl)[4-(4-pyridylmethyl)-phthalazin-1-yl]ammonium

hydrogen succinate and as compound II sTie2, mAB 4301-42-35, scFv-tTF and/ or L19 scFv-tTF conjugate.

19. Pharmaceutical compositions according to claims 1-17 which comprise as
5 compound I mAB 4301-42-35 and as compound II sTie2, and/ or scFv-tTF conjugate.

20. Pharmaceutical compositions according to claims 1-17 which comprise as
compound I scFv-tTF conjugate and as compound II sTie2 and/ or mAB 4301-
10 42-35.

21. Pharmaceutical compositions according to claims 1-17 which comprise as
compound I L19 scFv-tTF conjugate and as compound II sTie2.

15 22. Use of pharmaceutical compositions according to claims 1-21, for the
production of a medicament for the treatment of tumors, cancers, psoriasis,
arthritis, such as rheumatoide arthritis, hemangioma, angiofibroma, eye
diseases, such as diabetic retinopathy, neovascular glaukoma, kidney
diseases, such as glomerulonephritis, diabetic nephropathie, malignant
20 nephrosclerosis, thrombic microangiopathic syndrome, transplantation
rejections and glomerulopathy, fibrotic diseases, such as cirrhotic liver,
mesangial cell proliferative diseases, arteriosclerosis, damage of nerve
tissues, suppression of the ascites formation in patients and suppression of
VEGF oedemas.